



An Impossible Balance: Antibiotic Resistance, Profits, and Public Health

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**An Impossible Balance:
Antibiotic Resistance, Profits, and Public Health**

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Abstract

The scientific mechanism for the development of antibiotic resistance in microbes has long been understood, and has long cautioned against the use of low doses of antibiotics insufficient to treat disease thoroughly. Despite this, low doses of antibiotics have, for nearly half a century, been given to food animals to promote faster growth and greater feed efficiency. Though this raises public health concerns, a complex political landscape has historically prevented these public health concerns from dominating regulatory policy, and continues to do so. This paper examines the scientific, political, and legal issues associated with the use of antibiotics in animal agriculture, with particular focus on FDA's historical and evolving role in regulating this issue, and concludes briefly with speculation about the future of this issue.

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I. Introduction

Since the mid-twentieth century, antibiotic drugs have been used to promote growth in meat-producing animals. For just as long, it has been understood that repeated use of antibiotic drugs will eventually lead to a decrease in efficacy of those drugs, as natural selection leads to more and more microbes that are resistant to the antibiotics. From a public health perspective, one must balance the present public health benefits of the use of antibiotics against the future public health consequences of resistance to those antibiotics.

In the context of animal agriculture, however, the consensus has long been that there are no benefits to public health of the use of antibiotics in low, constant doses (sometimes called “sub-therapeutic” or “non-therapeutic” use) to promote growth. Instead, it has been acknowledged that the only known benefit to such use is economic: that increasing feed efficiency and decreasing the amount of time it takes to for animals to reach their slaughter weight boosts profit margins.¹ The method, if used widely, could also decrease meat prices, another economic benefit, though this benefit would accrue to the general public rather than to the producers.

From a public health perspective, however, we must face the risks of the development of antibiotic resistance in microbes that cause human diseases, many of which live in meat animals. This forces us to confront the task of balancing public health risks against economic benefits accrued to producers (potentially larger profit margins) and consumers (cheaper meat). This raises the very difficult question of how one could balance two concepts that operate in separate

¹ This increase in profits may only be temporary, however; the method could eventually become widespread, and competition and the subsequent increase in supply would decrease the market price of the product.

realms of incomparable values; as Roger Traynor once famously asked, “Can you weigh a bushel of horsefeathers against next Thursday?”²

Historically in the United States, we have come down on the side of the economic benefits, primarily on the grounds that the benefits are more demonstrable and certain than the risks, which are deemed by industry to be too speculative. The FDA and Congress have also been historically reluctant to act on the risks, though recent exceptions have demonstrated increasing scrutiny of this issue, indicating that the balancing calculus may in the process of changing.

This paper begins by reviewing the evolution of scientific knowledge pertaining to the issues of antibiotic resistance and the transference of drug-resistant disease microbes from food-producing animals to humans. This is followed by a brief overview of the political entities that have dealt with the issues, including industry groups and consumer advocates. This scientific and political background sets the stage for Part III of this paper, which consists of a historical treatment of the regulation of antibiotics used in animal feed. Part IV speculates over the best policies for FDA to pursue, grounded in the scientific knowledge and the legal and practical frameworks discussed in the paper, and Part V concludes.

II. Background

A. Scientific Background

The basic scientific concept relating to the issue of antibiotic resistance is certainly not new. The notion that evolution occurs through natural selection in response to the environment’s

² Brainerd Currie (*The Disinterested Third State*, 28 LAW & CONTEMP. PROBS. 754 (1963)) traces this quote back to Prosser (*Res Ipsa Loquitur in California*, 37 CALIF. L. REV. 183, 225 (1949)), in its original form asking how “ten pounds of sugar can be weighed against half-past two in the afternoon,” which in turn is attributed to an unidentified English judge.

selective pressures is a well-accepted and central tenet of modern biology.³ Thus, across the backdrop of an antibiotic agent that kills microorganisms through a certain biochemical mechanism, successive generations of those microorganisms will become increasingly resistant against that agent, and likely also against similar agents that operate through a similar mechanism. By the mid-twentieth century, this mechanism of bacterial evolution was demonstrated experimentally.⁴

Robust debate relating to this issue is taking place in the medical literature with respect to prescriptions of antibiotics to humans, which is widely accepted as contributing to antibiotic resistance in human diseases. Without a doubt, prescriptions to humans are the largest factor responsible for the evolution of human disease to resist antibiotics. The debate over this issue involves public health balancing, weighing the public health benefits to present patients against public health risks to future patients, as well as considerable discussion over treatment protocols and other ways to deal with this threat.⁵ Although the use of antibiotics in humans is the primary mechanism for the evolution of antibiotic-resistant human diseases, this paper does not address these difficult issues; the discussion here is limited to the use of antibiotics in agriculture.⁶

One lesson from the human experience with antibiotics, however, may be transferred to animals, and that is the importance of dose. The well-known treatment protocols in humans

³ See generally Charles Darwin, ON THE ORIGIN OF SPECIES.

⁴ Salvador Luria & Max Delbrück, *Mutations of Bacteria from Virus Sensitivity to Virus Resistance*, 28 GENETICS 491 (1943).

⁵ See generally Fred Tenover, CDC Director of the Office of Antimicrobial Resistance, *Testimony before the U.S. Senate Health, Education, Labor and Pensions Committee : CDC's Role in Monitoring and Preventing Antimicrobial Resistance*, revised April 19, 2011, available at <http://www.hhs.gov/asl/testify/2008/06/t20080624e.html> .

⁶ For a paper discussing the many difficult issues raised by human use of antibiotics, see Joseph Gottfried, *History Repeating? Avoiding a Return to the Pre-Antibiotic Age* (2005) in Chapter VI.C.3 of the Food and Drug Law Electronic Book.

involve using a large enough dose to eradicate the disease-causing microbe, for a sufficient period of time to ensure that the microbes have all been eradicated. Anything less creates the risk of selecting for antibiotic-resistant bacteria, as has long been recognized.⁷ In the context of agriculture, this is a strong theoretical reason to believe that the low-level doses used for growth promotion pose a much greater hazard to public health than the more concentrated doses used to treat disease or prevent the spread of an outbreak of disease.

But with respect to the use of antibiotics in the context of agriculture, there is somewhat less of a consensus regarding the magnitude and nature of the problem than there is for human use. Although defenders of the practice of administering antibiotics to food animals do not usually deny the theoretical premise—that exposure to antibiotics exerts selection pressure that causes subsequent generations of microbes to be resistant to them—they tend to question whether a threat to human health can be conclusively demonstrated. The causal link between the evolution of antibiotic-resistant microbes in animals and corresponding antibiotic-resistant disease in humans is indeed difficult to demonstrate; though circumstantially the evidence may be strong, often other origins of the disease cannot be definitively ruled out. Advocates for use

⁷ In Alexander Fleming's Nobel Lecture, in which he recounted the story of the discovery of penicillin, he gave this caution:

It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant. Here is a hypothetical illustration. Mr. X. has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies. Who is primarily responsible for Mrs. X's death? Why Mr. X whose negligent use of penicillin changed the nature of the microbe.
Moral: If you use penicillin, use enough.

Alexander Fleming, *Nobel Lecture*, Dec. 11, 1945, available at nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf

in animals also tend to question whether the evolution of antibiotic resistance in particular strains of disease-causing microbes actually has any practical implications for public health. One such argument, for example, is that some common diseases usually resolve without antibiotic intervention, and thus antibiotic resistance in these strains of disease does not pose a human health risk.

Skeptics of regulation in this arena are undoubtedly correct about the existence of gaps in scientific knowledge on this issue. A major reason for this is the complexity of the problem: tying a causal link, between particular uses of antibiotic and particular antibiotic-resistant foodborne (or other) illnesses, is a very difficult task when a very complex food supply chain stands between the two. There are also problems of data collection on both ends of the chain. Patients rarely have the pathogens that cause their diseases cultured. And many instances of foodborne illness resolve with time, regardless of whether the patient receives antibiotics; this can help mask the emergence of antibiotic-resistant pathogens that pose greater risk to members of vulnerable populations, such as children or the elderly.

Further, very little is known empirically about how much of each antibiotic is used in animal agriculture, and in what amounts, and for what purpose (disease treatment, disease prevention, or growth promotion). Industry is not forthcoming with that data, which is protected as private business information, and in recent years industry has been generally loathe to acknowledge that antibiotics are used for growth promotion at all, having attempted to rebrand such uses as “health maintenance” or “disease prevention.”⁸ Until just last year, there were no

⁸ The only mention of the phrase “growth promotion” on the website of the Animal Health Institute, the most important and vocal trade group for animal drugs, claims that growth promotion is synonymous with health maintenance: “health maintenance purposes, *also called* growth promotion. (See definition for health maintenance.)” According to the Animal Health Institute, the definition of health maintenance is: “Shifting the population balance of the microflora in the gastrointestinal tract, thus

reliable figures even for the *total* amount of antibiotics used in animal agriculture, and the two primary estimates, given by a major consumer group on the one hand and a major industry group on the other, differed by several million pounds.

Finally, and perhaps most surprisingly, the exact mechanism by which antibiotics promote growth in food animals is itself not understood and subject to debate,⁹ even though the fact that they do promote growth has been known for more than half a century.¹⁰

So what do we know? Based on the data made available by FDA in December 2010, animal agriculture consumes roughly 29 million pounds of antibiotics per year.¹¹ To put this in perspective, FDA estimates that the total amount of antibiotics prescribed to *humans* in the same year was 7 million pounds;¹² based on these figures, more than 80% of annual antibiotic use by weight in the United States goes to animal agriculture rather than human uses.

And despite all the difficulties in proving causation, three case studies of three outbreaks

improving nutrient utilization and resulting in healthy growth. Feed efficiency and average daily gain are indicators of response.” This is a naked attempt to couch an economic benefit in the language of health. “AHI: Key Industry Terms,” www.ahi.org/content.asp?contentid=718 (accessed 5/6/2011).

⁹ Although the industry’s definition of “health maintenance,” *supra* note 8, claims that the mechanism of growth promotion involves action on gastrointestinal bacteria, there is no scientific consensus that this is the mechanism. Other proposed mechanisms exist, including, for example, mechanisms involving shifts in energy metabolism unrelated to microbes.

¹⁰ See P.R. Moore et al., *Use of sulfasuxidine, streptothricin, and streptomycin in nutritional studies with the chick*, 165 J. BIOL. CHEM. 437 (1946) (showing growth promotion effect in poultry); T.J. Cunha et al., *Effect of aureomycin and other antibiotics on the pig*, 9 J. ANIMAL SCI. 653 (1950) (showing growth promotion effect in swine); J.K. Loosli & H.D. Wallace, *Influence of APF and aureomycin on the growth of dairy calves*, 75 PROC. SOC. EXPERIMENTAL BIOL. MED. 531 (1950) (showing growth promotion effect in cattle).

¹¹ FDA CTR. FOR VETERINARY MEDICINE, “2009 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals” at Tbl. 1, *available at* www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM231851.pdf (domestic total of 13,067,100 kg/yr, converted to pounds on the basis of 2.20 lbs/kg).

¹² Ralph Loglisci, *Animals Consume Lion’s Share of Antibiotics*, Food Safety News (Dec. 27, 2010) (citing spokesperson at FDA’s Office of Surveillance and Epidemiology), *available at* www.foodsafetynews.com/2010/12/animals-consume-lions-share-of-antibiotics/.

in the late nineties were perhaps responsible for increasing public and governmental awareness and scrutiny of this issue. Perhaps most prominent was a Danish study that was able to trace a particularly bad *Salmonella* outbreak (resulting in two deaths) of a strain that was resistant to many drugs, including fluoroquinolones (specifically the powerful drug ciprofloxacin) through the supply chain to a particular herd of swine that carried the identical multidrug-resistant bacteria.¹³ Another study,¹⁴ this one domestic, found that in Minnesotans suffering from *Campylobacter* infections, the rate at which those infections were resistant to ciprofloxacin increased from 1.3% in 1992 to 10.2% in 1998; this was correlated with the fact that a related antibiotic, enrofloxacin, was approved for use in U.S. poultry in 1996.¹⁵ And a 2000 study of an isolated case alarmed the pediatric medicine community by demonstrating the possibility of resistance to cephalosporins, which are essential to treating serious diseases in children; the Nebraska boy in this case apparently acquired the drug-resistant strain from direct contact with cattle (on which the identical strain was found), while a related drug, ceftiofur, is approved for use in cattle.¹⁶

Since this scientific awakening of sorts at the end of the 20th Century, data have continued

¹³ Kåre Mølbak et al., *An Outbreak of Multidrug-Resistant, Quinolone-Resistant Salmonella enterica Serotype Typhimurium DT104*, 341 N. ENGL. J. MED. 1420 (1999).

¹⁴ Kirk Smith et al., *Quinolone-Resistant Campylobacter jejuni Infections in Minnesota, 1992–1998*, 340 N. ENGL. J. MED. 1525, 1530 (1999). This finding is dwarfed by the experience of Spain, where regulation of use of the drugs was considerably more lenient in the early 1990s; after introduction of fluoroquinolones in Spanish poultry in 1990, fluoroquinolone resistance in clinical samples of *Campylobacter* spiked from less than 10%, pre-1990, to more than 40% in 1991 and increased to 85% by 1996. Data reproduced in Ellen Silbergeld, Jay Graham, & Lance Price, *Industrial Food Animal Production, Antimicrobial Resistance, and Human Health*, 29 ANNUAL REV. PUBLIC HEALTH 151, 158 (2008).

¹⁵ This and other evidence led the FDA to withdraw the approval of enrofloxacin for use in poultry, see Part III.C *infra*.

¹⁶ Paul Fey et al., *Ceftriaxone-Resistant Salmonella Infection Acquired by a Child from Cattle*, 342 N. ENGL. J. MED. 1242 (2000).

to develop that showed similar trends between the introduction of antibiotics for agricultural use and the increased rate of antibiotic-resistant bacteria in clinical isolates from sick patients.¹⁷ A recent study got quite a response in the media by testing meat sold in the U.S., finding *Staphylococcus aureus* on 47% of samples, with 52% of these exhibiting multidrug-resistance.¹⁸ This only added to studies showing other species of multidrug-resistant bacteria present on U.S. meat.¹⁹ Numerous other case studies have demonstrated other routes of transmission from animals to humans, including direct and community-based contact²⁰ and various environmental mechanisms, through waste, air, water, soil, food crops, and intermediate disease vectors such as flies.²¹

The evidence, with a few exceptions, is largely what a lawyer would call “circumstantial,” yet the scientific weight continues to mount into scientific consensus among public health professionals.²² And part of the urgency comes from the fact that new antibiotics are becoming hard to discover or develop; in the 1980s, new antibiotics were approved at a rate of 3 per year, while in the 21st century through 2007, slightly more than one per year were approved; only two were approved in the years 2005, 2006, and 2007 combined.²³ From a scientist’s and public health professional’s perspective, the rational course of action in the face of

¹⁷ See Silbergeld et al., *supra* note 14, at 157–58 (citing studies).

¹⁸ Andrew Waters et al., *Multidrug-Resistant Staphylococcus aureus in US Meat and Poultry*, 52 CLINICAL INFECTIOUS DISEASES 1227 (2011).

¹⁹ See *id.* at 1227 (citing FDA NARMS annual report); see also Silbergeld et al., *supra* note 14, at 158–59 (citing studies).

²⁰ Silbergeld et al., *supra* note 14, at 159 (citing case studies).

²¹ *Id.* at 159–61 (citing numerous references).

²² For a typical editorial with a title that says it all, see Sherwood Gorbach, *Antimicrobial Use in Animal Feed – Time to Stop*, 345 N. England J. Med. 1202 (2001).

²³ EXTENDING THE CURE, Policy Brief 6 at 2 (May 2008), available at http://www.extendingthecure.org/sites/default/files/Policy_Brief6_May08_newdrugs.pdf.

these facts is to act to preserve these precious resources for treatment, and not risk squandering them for economic benefits. With this background in mind, this paper now begins to examine the politics behind this issue and why, historically, the predominant scientific and public health view has not commanded our public policy.

B. The Political Landscape

1) Federal Government Agencies

The Food and Drug Administration (“FDA”) is the main entity in the United States charged with evaluating the safety of antibiotics and regulating their use. FDA’s authority in this regard derives from the Food, Drug and Cosmetic Act (FD&C Act), which defines a “drug” as an article “intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man *or other animals*.”²⁴ The FDA approves only those drugs for use in animals that have been shown to be “safe and effective,” with respect to the *animal’s* health.²⁵ However, because the animal will eventually be used as human food, FDA also must consider whether the use of the antibiotic somehow could lead to a risk in *human* health. A primary consequence of this is that FDA sets antibiotic residue limits for meat.²⁶ But FDA’s duty is considerably broader than protecting against residues in food: food from food animals must be completely safe for human consumption. (The debate on the exact nature of this safety standard will be discussed in further detail in Part III, *infra*.) If using the antibiotic could lead to the evolution of antibiotic-resistant disease-causing microbes in the food animal, FDA may potentially choose not to approve the

²⁴ FDCA § 201(g), 21 U.S.C. § 321(g) (2010).

²⁵ See FDCA § 512, 21 U.S.C. § 360b; 21 C.F.R. § 514.1(b)(8); *Stauber v. Shalala*, 895 F. Supp. 1178, 1190–91 (W.D. Wisc. 1995).

²⁶ See generally 21 C.F.R. part 556, Tolerances for Residues of New Animal Drugs in Food (2010).

drug at all, basing its decision on public safety concerns.

FDA's role is thus the most crucial and direct among the federal governmental agencies, acting as a gatekeeper and prescriber of standards of use of antibiotics administered to animals. Other government bodies also weigh in on the issue, though none have the regulatory authority of FDA. The U.S. Department of Agriculture ("USDA"), for instance, does not have any regulatory authority over the use of antibiotics given to animals, although USDA does occasionally issue guidance to producers of food animals regarding antibiotic use.²⁷ Given USDA's statutory role as an advocate for producers, however, one would expect them to regulate antibiotic use only insofar as it serves the interests of the food animal producers; public health concerns, aside from meat quality, is not within their general jurisdiction.²⁸

The Centers for Disease Control and Prevention ("CDC") has been a relatively consistent government voice urging the limitation of the use of antibiotics in food animals, particularly cautioning against the use of antibiotics for growth promotion. They have also occasionally opposed approval of particular *therapeutic* antibiotics for use in food animals, most notably enrofloxacin, which FDA approved for therapeutic use and then later withdrew, *see* Part III.C., *infra*. They have also, since 1996, maintained the National Antimicrobial Resistance Monitoring System ("NARMS"), which gathers crucial data on antibiotic resistant diseases and releases annual reports.²⁹ CDC is also one of the co-chairs (with FDA and the National Institutes of

²⁷ *See, e.g.*, U.S. DEP'T OF AGRICULTURE, ANIMAL AND PLANT HEALTH INSPECTION SERVICE, Antimicrobial Resistance Issues in Animal Agriculture (May 2007), *available at* http://www.aphis.usda.gov/animal_health/emergingissues/downloads/antiresist2007update.pdf.

²⁸ But note, as one of the many examples of the sometimes inexplicable and illogical carving up of authority between FDA and USDA, that animal biologics (e.g. vaccines) are regulated by USDA.

²⁹ *See, e.g.*, CTRS. FOR DISEASE CONTROL & PREVENTION, National Antimicrobial Resistance Monitoring System Enteric Bacteria (NARMS): Human Isolates Final Report 2008 (2010), *available at* http://www.cdc.gov/narms/annual/2008/NARMS_2008_Annual_Report.pdf.

Health (“NIH”)) of the Interagency Task Force on Antimicrobial Resistance, established in 1999 in response to a congressional hearing on the topic.³⁰

2) Industry and Trade Groups

Producers of antibiotic drugs have ensured that their voices are heard in the debate over limiting the uses of their products. One trade organization called the Animal Health Institute (“AHI”) has been particularly vocal. AHI discloses its member companies,³¹ which number twenty-four in all, including the major pharmaceutical companies such as Abbott, Bayer, Merck, Novartis, and Pfizer. AHI’s stated chief goal is to “advocate . . . with government agencies, creating a stable regulatory environment based on sound science.”³² Their positions have mirrored those of industry generally by opposing any limitation on use of antibiotics in food animals. Notably, AHI even intervened as a non-party participant (i.e. supporting Bayer, the actual respondent) in FDA’s proceedings to withdraw the approval of the New Animal Drug Application for enrofloxacin; *see* Part III.C, *infra*.

The American Veterinary Medical Association (“AVMA”), a professional organization representing veterinarians with the stated mission of “advanc[ing] the veterinary medical profession,”³³ acting as a “collective voice for its membership and for the profession,”³⁴ whose

³⁰ The Interagency Task Force developed a Public Health Action Plan in 2001, and released Annual Reports through 2008. The Interagency Task Force is still active and in the process of revising its action plan, a draft of which is open for public comment; *see* CDC, *Draft Action Plan—A Public Health Action Plan to Combat Antimicrobial Resistance*, 76 Fed. Reg. 14402 (Mar. 16, 2011).

³¹ *See* Animal Health Institute Member Companies, *available at* <http://www.ahi.org/content.asp?contentid=759> (accessed 5/6/2011).

³² “About AHI,” <http://www.ahi.org/content.asp?contentid=697> (accessed 5/6/2011).

³³ “About the AVMA: Mission / Objective” http://www.avma.org/about_avma/whoweare/mission.asp (accessed 5/6/2011).

³⁴ “About the AVMA: Who We Are” http://www.avma.org/about_avma/default.asp (accessed 5/6/2011).

members work in “private and corporate practice, government, industry, academia, and uniformed services.”³⁵ While not strictly an “industry” group, AVMA is clearly a group that has an interest in wider availability of animal drugs; their policy statements, too, have consistently weighed against any limitations whatsoever on the use of antibiotics in food animals, aside from occasional tepid endorsements of some of “advisory” guidelines.

In contrast to these private interests, at least one other, major private interest has taken up the cause of eliminating non-therapeutic uses of antibiotics. McDonald’s Corporation has established as its preferred policy that “antibiotics belonging to classes of compounds currently approved in one or more countries worldwide for use in human medicine [be] prohibited when used solely for growth promotion purposes.”³⁶ McDonald’s requires its direct suppliers to adhere to this policy, and states that it will otherwise be a favorable factor in making other supply decisions (i.e. for suppliers not in a “direct” relationship with McDonald’s).³⁷ While McDonald’s does not give data that would allow one to assess the real impact of its policy, we should nonetheless give strong consideration to the possibility that, in the company’s words, “voluntary, market-based actions can complement ongoing activities to address the issue of antibiotic resistance.”³⁸ Their policy also demonstrates that private interests can sometimes advance the public interest through the private market.

Unsurprising, but worth noting, is that trade organizations dealing with human medicine

³⁵ *Id.*

³⁶ MCDONALD’S CORP., “McDonald’s Global Policy on Antibiotic Use in Food Animals” 1 (June 2003), *available at* http://www.aboutmcdonalds.com/etc/medialib/aboutMcDonalds/socialresponsibility.Par.33574.File.dat/antibiotics_policy.pdf.

³⁷ *Id.* at 3.

³⁸ *Id.* at 1.

have tended to oppose the use of antibiotics in animals. For example, the American Medical Association (“AMA”) has opposed approval of specific drugs for use in animals,³⁹ openly opposed use of antibiotics as growth promoters,⁴⁰ and supported legislation that would phase out all use of antibiotics for growth promotion in animals.⁴¹ Other human medicine-oriented trade groups have aligned themselves similarly (e.g. the American Public Health Association, the American College of Preventative Medicine, the Ambulatory Pediatric Association, and the American Nurses Association have at various released statements critical of the use of antibiotics in animal agriculture.)

3) Consumer-Oriented Public Interest Groups

The Union of Concerned Scientists (“UCS”) has been the primary consumer-oriented nonprofit that has drawn attention to issues of antibiotic resistance in many contexts, including animal agriculture. Notably, UCS was the first entity to provide a transparent, credible estimate of antibiotic use in agriculture when such figures were entirely unknown to the world.⁴² (FDA now collects data on total sales of animal antibiotics as a mandatory requirement of the Animal Drug User Fee Act Amendments of 2008;⁴³ UCS’s 2001 estimate of 29.6 million pounds per

³⁹ Letter from Michael Maves, AMA’s Executive Vice President and CEO, to the Commissioner of Food and Drugs, March 19, 2007 (opposing NADA for use of cefquinome in cattle), *available at* www.keepantibioticsworking.com/new/resources_library.cfm?refID=97841.

⁴⁰ AMA Policy Statement H-440.895 (Resolution 508, April 2001), *available at* www.ama-assn.org/resources/doc/PolicyFinder/policyfiles/HnE/H-440.895.htm.

⁴¹ Letter from Michael Maves, AMA’s Executive Vice President and CEO, to Representative Louise Slaughter, April 9, 2009 (supporting H.R. 1549 “Preservation of Antibiotics for Medical Treatment Act of 2009”), *available at* www.keepantibioticsworking.com/new/resources_library.cfm?refID=106530.

⁴² See Margaret Mellon, Charles Benbrook, & Karen Lutz Benbrook, HOGGING IT! ESTIMATES OF ANTIMICROBIAL USE IN LIVESTOCK (2001). In this report, UCS documented the unavailability of the data, and questioned the reliability of AHI’s extremely low estimate of 17.8 million pounds for all animal uses, which AHI gave without stating its factual basis or methodology. *Id.* at 58.

⁴³ 110 P.L. 316, amending in relevant part FDCA § 512, 21 U.S.C. § 360b.

year⁴⁴ is remarkably close to the sales figures actually tabulated by FDA in 2009, 28.8 million pounds per year.⁴⁵) In particular, UCS’s advocacy position is generally that classes of antibiotics that are important to the treatment of human disease should not be allowed for “subtherapeutic” or growth promotion purposes,⁴⁶ or more cautiously, that FDA, USDA and CDC need to study the matter much more quickly, rigorously and critically.⁴⁷

The Center for Science in the Public Interest (“CSPI”) is another prominent consumer group known for its advocacy role with respect to the FDA. CSPI has repeatedly urged the FDA to withdraw approval of certain antibiotics currently approved for growth promotion purposes, specifically focusing on those antibiotics from classes that are important to human medicine.⁴⁸ FDA has not taken action on such calls; for example, CSPI’s 1999 petition singled out virginiamycin, a streptogramin (a class of drugs used to treat human diseases, for which few or no alternatives exist⁴⁹) which was (and still is) approved for growth promotion in swine, poultry and cattle.⁵⁰

In 2006, a grant from the Pew Charitable Trusts established, in partnership with Johns Hopkins Bloomberg School of Public Health, the Pew Commission on Industrial Farm Animal Production. In April 2008, the Commission released a report recommending the restriction of

⁴⁴ Mellon et al., *supra* note 42, at 60.

⁴⁵ *See supra* note 11.

⁴⁶ Mellon et al., *supra* note 42, at 6–7.

⁴⁷ *Id.* at 64–65.

⁴⁸ *See, e.g.*, FDA, Second Tentative Response to CSPI’s Citizen Petition, FDA Docket No. 99P-0485 (Feb. 28, 2001), *available at* <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CVM/CVMFOIAElectronicReadingRoom/UCM129142.pdf>.

⁴⁹ Mellon et al., *supra* note 42, at 108.

⁵⁰ *See* 21 C.F.R. § 558.635 (d)(1)(iv)–(v); § 558.635 (d)(2)(i)–(ii), (iv); § 558.635 (d)(3)(i), (iii) (2010).

use of antimicrobials to reduce the risk of antimicrobial resistance to medically important antibiotics, including the recommendation that FDA “phase out and ban use of antimicrobials for nontherapeutic (i.e. growth promoting) use in food animals”⁵¹ Notably, however, the Pew Commission’s recommendations were based not just on public health, but also on environmental impact, animal welfare, and the social and economic effects of concentrated agriculture on rural America; while analyzing antibiotic use from the perspective of all these effects is, in my view, an admirable and important task, consideration of all of them is outside the scope of this paper.

But there are also other examples of public interest groups which are not focused primarily on human health taking up the issue of antibiotic use in animals, including notable environmental groups. In a 1984 petition, the National Resources Defense Council (“NRDC”) asked that New Animal Drug Applications be suspended on an imminent harm theory; after a hearing⁵² their petition was denied.⁵³ Another group, the Environmental Defense Fund, joined CSPI’s March 9, 1999 petition.⁵⁴ And, occasionally, animal rights groups have raised the issue of antibiotic use as an animal welfare issue, as they can be used to promote more intensive farming.⁵⁵ But the relative impact of environmental and animal rights groups is certainly less than the consumer- and science-oriented groups that have continued to play a large role in framing the debates.

⁵¹ See PEW COMM. ON INDUSTRIAL FARM ANIMAL PRODUCTION, *Putting Meat on the Table: Industrial Farm Animal Production in America* 61 (2008).

⁵² 49 Fed. Reg. 49645 (Dec. 21, 1984).

⁵³ U.S. DEP’T OF HEALTH AND HUMAN SERVS., Decision of the secretary denying petition to suspend new animal drug applications for subtherapeutic uses of penicillin and tetracyclines in animal feed, Docket No. 84P-0399 (Nov. 19, 1985)

⁵⁴ See FDA, *supra* note 48.

⁵⁵ See, e.g. *Animal Legal Defense Fund Boston v. Provimi Veal Corp.*, 626 F. Supp. 278 (D. Mass. 1986).

4) Congress

Congress is, theoretically, the most powerful voice of all in this process, having the capability to amend the FD&C Act, which it does frequently for various purposes. However, when it comes to antibiotic use in animal agriculture, Congress has not made any great interventions.

One important role Congress has served, however, is the direction of its research arm, the Government Accountability Office (formerly the General Accounting Office). Two recent reports have been influential,⁵⁶ the first of which led in part to the establishment of the Interagency Task Force on Antimicrobial Resistance, *see supra* Part II.B.(1).

In terms of legislation, Democratic Congresswoman Louise Slaughter has repeatedly proposed legislation that would forbid the use of antibiotics for growth promotion purposes in U.S. livestock.⁵⁷ Overall, such legislation seems unlikely to pass; it had, by most accounts, its most favorable opportunity with the large Democratic majority in the 111th Congress, when it advanced to Committee Hearings on July 13, 2009. Even then, however, pressure on representatives from significant meat-producing states was enough to prevent any action on the bill. One can speculate that it would take a massive, widely-publicized drug-resistant disease outbreak, with a smoking gun at the feet of a particular herd of meat animals, before Congress would pass such legislation. This may be another instance of a common political scenario: the

⁵⁶ GENERAL ACCOUNTING OFFICE, ANTIBIOTIC RESISTANCE: FEDERAL AGENCIES NEED TO BETTER FOCUS EFFORTS TO ADDRESS RISK TO HUMANS FROM ANTIBIOTIC USE IN ANIMALS, GAO-04-490 (Apr. 22, 2004); GENERAL ACCOUNTING OFFICE, FOOD SAFETY: THE AGRICULTURAL USE OF ANTIBIOTICS AND ITS IMPLICATIONS FOR HUMAN HEALTH, GAO-RCED-99-74 (Apr. 28, 1999).

⁵⁷ Most recently, Preservation of Antibiotics for Medical Treatment Act of 2011, 112th Cong. H.R. 965 (introduced 3/9/2011).

interest of the meat producers is too strong, and not worth defying for the sake of members of the broader public, for whom the issue barely registers. The issue has a few strong supporters on one side, such as Rep. Slaughter, and a few equally staunch supporters on the other side, for instance Rep. Steve King (Republican of Iowa),⁵⁸ and a large swath of Congress for whom taking a side has few advantages.

5) Internationally

The World Health Organization (“WHO”) has been important for its role comparing the different experiences of countries that have taken different approaches to the problem of antibiotic use in food animals.⁵⁹ WHO recently highlighted the issue by declaring antimicrobial resistance generally to be the theme of 2011 World Health Day.⁶⁰ Generally, WHO has advocated “terminat[ing] non-therapeutic use of antimicrobials, such as the use of antimicrobials as growth promoters.”⁶¹ In this respect it has been similar to domestic health advocacy organizations, but has the distinction of being cited frequently for a more global view.

III. History of Animal Antibiotic Regulation in the United States

A. Early Regulation

As described in Parts I and II.A, *supra*, the potential for antibiotic resistance, particularly

⁵⁸ Steve King, “Farmers, not bureaucrats, know best,” The Hill’s Congress Blog (Jan. 26, 2010), *available at* <http://thehill.com/blogs/congress-blog/politics/78037-farmers-not-bureaucrats-know-best-rep-steve-king>.

⁵⁹ Discussed in Part IV, *infra*.

⁶⁰ WHO, Press Release: Urgent action necessary to safeguard drug treatments (April 6, 2011), *available at* www.who.int/mediacentre/news/releases/2011/whd_20110406/en/index.html.

⁶¹ WHO, World Health Day 2011 Policy Brief 4D, at 2, *available at* www.who.int/world-health-day/2011/presskit/whd2011_fs4d_subanimal.pdf.

resulting from constant, low-dose exposure, was recognized almost as early as antibiotics themselves were discovered.⁶² In 1970, the FDA Commissioner established a Task Force to study the risks associated with the use of antibiotics in animal feed and to make recommendations.⁶³ The Task Force concluded from the available evidence that the “prevalence of multiresistant R-factor bearing pathogenic and non-pathogenic bacteria in animals has increased and has been related to the use of antibiotics and sulfonamide drugs[,]” and that there “has been an increase in the prevalence of antibiotic and sulfonamide resistant bacteria in man.”⁶⁴ The Task Force further concluded, based on “extensive documentation,” that “[h]uman illnesses and death have been reported due to both antibiotic-sensitive and antibiotic-resistant bacteria of animal origin.”⁶⁵ The Task Force recommended that the FDA revoke all permitted use of antibiotics for growth promotion, and only to allow such drugs to be used subtherapeutically again if they were found to satisfy the Task Force’s Guidelines for such use.⁶⁶ Like most public health advocates have maintained for decades, the 1970 Task Force apparently gave considerable weight to the evidence and theory that low-level, constant doses of antibiotics will lead inevitably to antibiotic resistant microbes.

It came as somewhat of a surprise, then, when the FDA Commissioner, just one year later, backpedaled considerably from the Task Force’s proposed approach. In contrast to the Task

⁶² See *supra* notes 4, 7 and accompanying text.

⁶³ FDA, “Antibiotic and Sulfonamide Drugs in Animal Feeds: Proposed Statement of Policy” 37 Fed. Reg. 2444, 2444 (Feb. 1, 1972).

⁶⁴ *Id.* at 2444–45.

⁶⁵ *Id.* at 2445.

⁶⁶ *Id.* The Guidelines themselves were, mysteriously, not reproduced in the Federal Register or proposed regulations, and only appeared in the Task Force’s Report to the Commissioner. However, it seems clear from the face of the regulation that the Task Force was most concerned with (1) whether the antibiotics in question belong to classes which are crucial for human medical use, and (2) whether evidence demonstrated that resistance to that antibiotic was not likely to endanger human health. *Id.*

Force's approach, in which antibiotics were to be delisted for subtherapeutic use until proven safe for such use, FDA's policy changed into the difficult balancing described in the Introduction to this paper, *supra*. "Safety," FDA's new policy stated, suddenly did not mean absence of human health risks; rather, it meant "the reasonable certainty in the minds of competent scientists that [use of the drug] is not harmful *when balanced against the benefits to be obtained from the drug*."⁶⁷ According to the new policy, the "benefits accrue in terms of efficient land usage, labor savings, and more efficient conversion of animal feed to animal protein, thereby making a major contribution to the abundance of food from animals."⁶⁸ And while the "Commissioner recognize[d] that difficult questions exist with respect to the benefit-risk analysis"⁶⁹ of safety against economic benefits, the new policy seemed to resolve these questions neatly in almost the same breath: a line in the sand was drawn, separating "potential and theoretical hazards" on the one hand from "a serious health hazard, [for which] withdrawal should immediately be ordered" on the other.⁷⁰ The Federal Register notice went on to declare that all of the hazards described by the Task Force fell into the former category: "Where, as here, only a potential or theoretical hazard is raised, which does not show that the drug is not shown to be safe, . . . the proper way to proceed is [by the NADA process] . . ."⁷¹ By drawing this line between "potential" and "serious" risks (though there is no reason principled a risk cannot be both at once), and by characterizing all of the Task Force's findings as the "potential and theoretical," the new policy placed a heavy thumb on the scale in favor of the economic benefits, and this thumb

⁶⁷ FDA, "Antibiotic and Sulfonamide Drugs in the Feed of Animals" 38 Fed. Reg. 9811, 9812 (Apr. 20, 1973) (emphasis added).

⁶⁸ *Id.*

⁶⁹ *Id.*

⁷⁰ *Id.* at 9813.

⁷¹ *Id.*

subsequently rested on the scale for decades. Further, by dismissing the “theoretical hazards” as hazards that “do[] not show that the drug is *not shown* to be safe,” the FDA arguably managed to flip the initial burden, which ordinarily is on the NADA applicant to demonstrate that the drug *is* safe; this should require that the NADA applicant affirmatively demonstrate that the “theoretical hazards” of resistance are indeed insignificant.

The new policy, however, required firms wishing to market their antibiotic products to comply with new filing requirements of safety data.⁷² Although the details filed by these entities are confidential, and although some products were apparently delisted (at least temporarily) for failure to comply with the regulatory requirements,⁷³ most firms were quickly able to get their products relisted (and some new products approved), including for growth promotion purposes.⁷⁴ The economic benefits of growth promotion carried the day, and the Task Force’s “potential and theoretical hazards” of resistance were apparently accorded no weight in the balance, being instead left behind to serve as a historical footnote.

A 1977 change in presidential administrations, however, brought a new Commissioner of Food and Drugs, Donald Kennedy. Commissioner Kennedy apparently deemed antibiotic resistance a significant threat, but apparently decided against taking up another battle to redefine the previous Commissioner’s theory of “safety” that incorporated economic benefits. Instead, he opted for a different tool of policy making, the relatively young National Environmental Policy Act, noting that antibiotic-resistant microbes in the environment generally would have an impact

⁷² The filing requirements remain codified, as amended, at 21 C.F.R. § 558.15.

⁷³ 39 Fed. Reg. 283 93 (Aug. 6, 1974); 41 Fed. Reg. 8282 (Feb. 25, 1976).

⁷⁴ 39 Fed. Reg. 28382 (Aug. 6, 1974); 40 Fed. Reg. 13959 (Mar. 27, 1975); 41 Fed. Reg. 8282 (Feb. 25, 1976).

on public health.⁷⁵ In light of this, the Commissioner planned to propose the banning of subtherapeutic use of penicillin;⁷⁶ as well as careful restrictions on tetracyclines.⁷⁷ Hearings went forward on this,⁷⁸ and GAO in effect encouraged the effort by criticizing FDA's failure to act sooner on subtherapeutic antibiotic use.⁷⁹ The effort apparently ultimately stalled with yet another change in administration, and in 1981 industry requested that approvals of new drugs resume as usual, a request that was granted;⁸⁰ a request to dismiss the previous administration's proceedings, however, was denied, and the proceedings have apparently been held in abeyance ever since, "pending completion of studies mandated by Congress."⁸¹ However, these two notices, published on the same day, make odd bedfellows, and one can legitimately question whether the latter was an effective termination of the proceedings, in light of the fact that the former notice demonstrated FDA's willingness to approve new penicillin and tetracycline containing drug premixes.

For the remainder of the 1980s and much of the 1990s, however, FDA did not revisit the subject; again, it seemed that the battle for public policy in this area had been won by industry,

⁷⁵ FDA, "Restriction of Subtherapeutic Use of Antibacterials in Animal Feeds: Intent to Propose Rules and Calls for Environmental Impact Data" 42 Fed. Reg. 27264, 27265 (May 27, 1977).

⁷⁶ *Id.* at 27264. Note that the FDA Task Force five years earlier targeted subtherapeutic use of penicillin in particular as posing a substantial risk; *see* FDA, *supra* note 63, at 2445 ("antibiotics which select for bacteria resistant to the antibiotics most critically needed for therapy of man and animals be *prohibited* from use in animal feeds. In this category at the present time are . . . penicillins . . .") (emphasis added).

⁷⁷ FDA, *supra* note 75, at 27265.

⁷⁸ *See* Peter Barton Hutt & Richard Merrill, FOOD AND DRUG LAW: CASES AND MATERIALS 652 n. 1 (2d ed. 1991) (citing numerous Federal Register notices corresponding to these hearings).

⁷⁹ GAO, NEED TO ESTABLISH SAFETY AND EFFECTIVENESS OF ANTIBIOTICS USED IN ANIMAL FEEDS, HRD-77-81 (Jun. 27, 1977).

⁸⁰ FDA, "New Animal Drugs for Use in Animal Feeds; Penicillin- and Tetracycline (Chlortetracycline and Oxytetracycline)-Containing Premixes" 48 Fed. Reg. 4490 (Feb. 1, 1983).

⁸¹ FDA, "Penicillin and Tetracycline (Chlortetracycline and Oxytetracycline) in Animal Feeds: Denial of Petitions" 48 Fed. Reg. 4554, 4555 (Feb. 1, 1983).

the balance of economic benefits definitively decided against the “theoretical” risks of harm from antibiotic resistance.

B. Increasing Scrutiny in the 1990s

While FDA’s interest in the subject seemed to wane, the interest of scientists, health professionals, and consumer groups seemed only to grow. The 1990s saw increasing number of independent articles published in peer-reviewed journals discussing the issues and mechanisms of antibiotic resistance.⁸² The Institute of Medicine prepared a report that included risk assessments that attempted to calculate the effect of antibiotic use in livestock on human health.⁸³

It was in response to another Institute of Medicine report in the early 1990s that CDC began laying the groundwork for the National Antimicrobial Resistance Monitoring System (NARMS).⁸⁴ NARMS annual reports began to shed light on the increasing rate of antibiotic resistance across the country, further propelling the issue into the public and Congressional debate. Consumer advocates prepared reports on antibiotic resistance and use in agriculture;⁸⁵ a coalition of consumer groups submitted a petition to FDA urging specific action on specific antibiotics;⁸⁶ and Congress held hearings on “Antimicrobial Resistance: Solutions to a Growing Public Health Problem,” ultimately creating the impetus for the creation of the Interagency Task

⁸² See, e.g. Mitchell Cohen, *Epidemiology of Drug Resistance: Implications for a Post-Antimicrobial Era*, 257 SCIENCE 1050 (1992); George Jacoby & Gordon Archer, *New Mechanisms of Bacterial Resistance to Antimicrobial Agents*, 324 N. ENGLAND J. MED. 601 (1991); Stuart Levy, *Editorial: Starting Life Resistance-Free*, 323 N. ENGLAND J. MED. 335 (1990).

⁸³ INSTITUTE OF MEDICINE, “Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed” (National Academies Press 1989);

⁸⁴ See CDC, “About NARMS” available at www.cdc.gov/narms/about_narms.htm.

⁸⁵ Ctr. For Science in the Public Interest, “Protecting the Crown Jewels of Medicine: A strategic plan to preserve the effectiveness of antibiotics” (1998); Mellon et al., *supra* note 42 (Union of Concerned Scientists report).

⁸⁶ See *supra* note 48.

Force on Antimicrobial Resistance.

The mounting pressure and attention may have, on its own, been enough to force FDA to take up the issue again. However, the “smoking gun”⁸⁷ of the late nineties case studies,⁸⁸ in particular the one demonstrating domestic strains of ciprofloxacin-resistant *Campylobacter*,⁸⁹ forced FDA’s hand and laid the ground for the first (and, to date, only) true battle over the revocation of a NADA antibiotic product.

C. FDA Takes Action: The Enrofloxacin Case

On October 4, 1996, FDA approved NADA 140-828, Bayer’s formulation of enrofloxacin, marketed under the trade name Baytril. Just over four years later, on October 31, 2000, FDA sought to withdraw that NADA, initiating the process by publishing a Notice of Opportunity for Hearing.⁹⁰ Bayer notified FDA that it would exercise its right to a hearing on November 29, 2000, setting up the first-ever adversarial proceeding to withdraw a NADA antibiotic.

FDA had a lot riding on this case. FDA undoubtedly wanted to demonstrate to the public and to industry that it was serious about antibiotic resistance and the associated risks to public health. Further, this adversarial proceeding presented a favorable opportunity to make good law for future agency action. Of course, the high stakes nature of this litigation would cut both ways, and given the unlikelihood of Congressional intervention in this area of law, FDA could equally be stuck with any unfavorable law made during the litigation. With limited resources and the

⁸⁷ This characterization attributed to Dr. Abigail Salyers in Dan Ferber, *Superbugs on the Hoof?* 288 *Science* 792, 792 (2000).

⁸⁸ *Supra* notes 13–14, 16.

⁸⁹ Smith et al., *supra* note 14.

⁹⁰ FDA, “Enrofloxacin for Poultry: Opportunity for Hearing (NOOH)” 65 Fed. Reg. 64954 (Oct. 31, 2000).

level of involvement that the case required, this one case, though formally only about one antibiotic's NADA, would stand for much larger questions of law and FDA's authority and ability to regulate antibiotics generally.

But FDA had reasons for optimism about its ability to win this particular case. On factual grounds, first, the study by Smith et al., noted *supra* at footnote 14, was fairly rigorous, testing the rate of resistance in actual instances of illness over time, pre- and post-approval. Second, years of scientific studies had shown that *Campylobacter* infections are primarily acquired from poultry and not other sources; the enrofloxacin formulation in question was approved only for poultry. Third, FDA finally had at its disposal, thanks to NARMS, a larger pool of data showing the incidence of fluoroquinolone-resistant *Campylobacter* infections over time. And finally, in what can be viewed in part as a collateral indication of the strength of the factual case, another manufacturer of another fluorquinolone product, Abbott Laboratories' sarafloxacin, took the unusual step of *voluntarily withdrawing* its NADAs for its sarafloxacin products.⁹¹

Perhaps more interesting than the seemingly solid factual grounds for the decision, however, was the potential establishment of FDA's legal authority to take this action. FDA took this opportunity to take a broader definition of "safety" in this context, citing, in a daring and perhaps controversial move, nothing more than *legislative history* from the FD&C Act's food additive provision, defining "safe" as "reasonable certainty of no harm."⁹² This is a far cry from the approach of balancing "reasonable certainty in the minds of competent scientists . . . against the [economic or other] benefits to be obtained from the drug"⁹³ discussed in Part III.A., above.

⁹¹ NADA 141-017 and 141-018; opportunity for hearing waived, *id.*; final withdrawal effective at 66 Fed. Reg. 21400 (Apr. 30, 2001).

⁹² 65 Fed. Reg. at 64956 (citing H. Rept. 2284, 85th Cong., 2d sess. 4095 (1958)).

⁹³ *Supra* note 67.

But here, too, the FDA had a favorable wind at its back in recent precedents. Specifically, Supreme Court cases since the 1980s have established that, generally speaking, federal agencies should not consider economic costs or benefits unless Congress has explicitly instructed them to do so, and particularly when agencies are dealing with safety and health.⁹⁴ Although not (yet) explicitly applied to the FD&C Act, this interpretative trend undoubtedly frowns upon the incorporation of economic benefits into the analysis of whether a drug or food additive is “safe.” Based on this legal trend, FDA would seem to have strong grounds for drastically narrowing the scope of the meaning of “safety” from the definition that had been, *de facto*, historically applied.

The litigation would also prove to be a legal test of how strictly bound by its prior actions FDA is. In this context, how easy is it for FDA to reverse its judgment from just a few years earlier that a certain drug is safe for use in animals? Under FD&C Act Section 512(e)(1)(B),⁹⁵ in order to withdraw approval for a NADA, FDA must show that “*new evidence* not contained in [the original] application or not available . . . until after such application was approved . . . evaluated together with the evidence available . . . when the application was approved, shows that [the] drug is not shown to be safe for use” (emphasis added). How much new evidence justifies withdrawal? And how can we make sense of this requirement in light of the fact that the mechanisms of antibiotic resistance, and the existence of the risk of transference of antibiotic-resistant pathogens to humans, have been known for decades? Can FDA simply change its mind whenever it wants on any given NADA, citing the latest scientific study as a piece of new evidence? This case may have had an exceptionally strong and current body of evidence, but the

⁹⁴ See *American Textile Manufacturers Institute v. Donovan*, 452 U.S. 490, 511-12 (1981) (rejecting OSHA’s attempt to incorporate economic cost-benefit into health assessments); *Whitman v. American Trucking Ass’n*, 531 U.S. 457, 471 (2001) (finding that EPA may not incorporate cost considerations into air quality standard setting absent Congressional intent that such an analysis be done).

⁹⁵ 21 U.S.C. § 360b(e)(1)(B).

legal ruling on the evidentiary issues would have implications for other potential agency actions.

The litigation itself was a drawn-out affair before an Administrative Law Judge. Though initiated in late 2000, Bayer's request for a hearing was not granted until early 2002, and soon thereafter the trade association AHI filed to participate in the hearing as well. By late 2002, all parties (including FDA) had submitted direct testimonial evidence in writing. In mid-2003, oral hearings were held at FDA for the purposes of cross-examination. Briefs were submitted by all parties, and on March 16, 2004, the ALJ published his initial decision in favor of FDA. Pursuant to FDA's rules for the proceeding, FDA and Bayer/AHI were permitted to file exceptions to the Initial Decision (in May 2004), and responses to each others' exceptions (in July 2004). Acting Commissioner Lester Crawford then issued FDA's Final Decision in July 2005, responding to the Initial Decision and Exceptions, and ruling in favor of the FDA, to withdraw approval of enrofloxacin.

A few things were noteworthy about the Commissioner's decision. First, on the issue of defining "safety," described above, the Commissioner took into account the Supreme Court case law regarding the permissibility of cost/benefit analysis, holding that FDA was not intended by Congress to engage in cost/benefit analysis when weighing safety.⁹⁶ However, the Commissioner did not limit this discussion to simply *economic* benefits and costs, but discussed whether *health* cost/benefit analysis was appropriate. He contrasted his position with that of the ALJ, who declined to weigh animal health and welfare benefits against risks to humans, though the ALJ was, clearly, technically correct on this point.⁹⁷ But the definition of "safe" as requiring "reasonable certainty of no harm" goes even further: according to the Commissioner, this

⁹⁶ FINAL DECISION OF THE COMMISSIONER, WITHDRAWAL OF APPROVAL OF THE NEW ANIMAL DRUG APPLICATION FOR ENROFLOXACIN IN POULTRY, Docket No. 00N-1571, at 102-03.

⁹⁷ *Id.* at 93.

definition does not even allow for the balancing of *human health* benefits against human safety concerns.⁹⁸ Presumably, then, even if the use of antimicrobials in animal feed were shown to have enormous human health benefits, the smallest of human health risks would control under the “reasonable certainty of no harm” standard. One can question the wisdom of this reading, but it is a logical reading of the stated definition, and it undoubtedly gives FDA broader power in the withdrawal process.

The Commissioner’s decision also shed some light on the evidentiary question. Bayer argued that, because FDA knew of the risks of antibiotic resistance before approving the drug, and had plenty of evidence before it that would caution against approving the drug, subsequent studies pointing to the same conclusion could not be considered “new evidence.” The Commissioner wisely rejected what he called a “content-driven definition of ‘new,’”⁹⁹ but unfortunately did not give much guidance on a better definition of “new,” stating merely that “[i]f the proffered evidence was developed or discovered after approval and is not the evidence relied on for approval, then it is ‘new.’”¹⁰⁰ This does not resolve some objections. Does the testimony of one more expert on the theoretical basis for resistance count as “new” evidence? A study that replicates the result of a previous study? A new meta-analysis of studies that were relied on in the original application? Some may argue that it is unclear under the Commissioner’s definition what constrains FDA from changing its mind at will, and what in the manner of “new evidence” FDA must ferret out in order to support its decision to withdraw the drug.

⁹⁸ *Id.* at 94.

⁹⁹ *Id.* at 86.

¹⁰⁰ *Id.* at 90.

Through the ALJ's and Commissioner's decision, FDA essentially won the case on every point of fact and law. Bayer could not obtain a stay of the judgment pending appeal, and as a result Bayer decided not to appeal at all.¹⁰¹ However, five years of litigation was a considerable use of FDA resources for the withdrawal of just one drug; although FDA has demonstrated it can succeed through this method, it lacks the time and resources to do so on a broad scale. Formally, this case proved to be a big victory for FDA, and perhaps it serves as a warning to industry that FDA has the power to take such action. Realistically, however, this cannot be the mechanism through which FDA controls the use of the dozens of antibiotics now permitted for use in animal agriculture.

D. Recent Developments

Since the initiation of the enrofloxacin action, FDA has released two major guidance documents for industry. Guidance for Industry #152 ("GFI #152")¹⁰² provides a detailed, comprehensive analysis of what FDA will consider, going forward, in decisions on NADAs for antibiotics. This guidance spells out what is expected of NADA filers in the brave new world in which the economic benefits of these drugs do not justify human health risks; FDA now wants details so that it can be reasonably certain of no harm in approving the new drugs for specific uses. One can wonder, and it remains an open question, whether, going forward under current policy, FDA will ever be willing to approve future NADAs for growth-promotion purposes, as opposed to disease treatment (one can speculate that the answer is perhaps yes, if, for example,

¹⁰¹ The costs and risks of appeal apparently were not justified in the absence of the ability to keep selling the drug while the case was on appeal. The inability to obtain a stay was a deciding factor in Bayer's decision not to appeal (Robert Nicholas, attorney for Bayer, personal communication).

¹⁰² FDA, "Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern," October 23, 2003.

the drug has no analogs used in human medicine).

Much more recently, and pertaining more relevantly to the dozens of drugs approved for use in animals before the release of GFI #152, is Draft Guidance #209.¹⁰³ This draft guidance document contains subtle hints that FDA is interested in adopting a more aggressive stance against antibiotics used at subtherapeutic levels. In particular, FDA states in this document:

In light of the risk that antimicrobial resistance poses to public health, FDA believes that the use of medically important antimicrobial drugs in food-producing animals for production purposes (e.g., to promote growth or improve feed efficiency) represents an injudicious use of these important drugs. Production uses are not directed at any specifically identified disease, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products.¹⁰⁴

The framework of the draft guidance, moreover, draws a line between drugs approved prior to GFI #152 and drugs approved pursuant to GFI #152; the latter have satisfied FDA's current policies, while the former (older drugs, including many approved for growth promotion purposes) are (implicitly) suspect in the eyes of FDA.¹⁰⁵

FDA is also urging the “phase-in [of] the practice of including veterinary oversight or consultation in the use of [medically important antibiotics].”¹⁰⁶ The fact that FDA would like to require veterinarians to be more involved is another sign of disapproval of the use of antibiotics indiscriminately for “production” purposes.

News reports also have provided insight into FDA's current thinking. Late last year, FDA officials reportedly told consumer advocates that it was attempting to obtain voluntary

¹⁰³ FDA, “Draft Guidance: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals,” June 28, 2010.

¹⁰⁴ *Id.* at 16.

¹⁰⁵ *Id.* at 15 (“VI. Status of FDA's Current Activities”).

¹⁰⁶ *Id.* at 17.

cooperation from industry, as an alternative to impossibly long legal processes (such as the enrofloxacin proceedings).¹⁰⁷ The draft guidance may have been merely the first step in attempting to coax “voluntary” action. Steve Roach, a consumer advocate, claimed that one official “seemed quite confident that some company was getting close to doing something,”¹⁰⁸ it is unclear what incentives the alleged company had to voluntarily move forward, but whatever this “something” was, it has not yet materialized in the several months since.

IV. Analysis of FDA Policy and Possible Approaches

FDA, through the enrofloxacin case, has established a strong legal precedent for its authority and ability to take action to withdraw currently approved antibiotics. However, its capability in this arena lacks practical strength: the entitlement to a hearing granted Bayer almost five more years of continued sales of their product. If the expected profits of the product exceed the amount it costs to hire lawyers for the administrative proceeding, the drug manufacturer can still come out ahead by opposing even the strongest case with the most minimal defense. Thus, the threat of withdrawal of individual drugs, one at a time, may not strike fear in the hearts of companies with robust animal drug sales.

Furthermore, even though FDA has changed its legal standards for what constitutes “safe” since many of antibiotics were approved for growth promotion, withdrawal of these drugs still requires a *factual* inquiry about whether there is sufficient and reliable new evidence that the use of the drugs is demonstrably less safe than it was at the time of its approval. This may not always be an easy burden to meet.

¹⁰⁷ Philip Brasher, “FDA trying voluntary restrictions on antibiotics,” Des Moines Register, Dec. 19, 2010.

¹⁰⁸ *Id.*

Analysis of FDA's current, internal plans to attain their policy objectives through "voluntary" compliance is a difficult task, perhaps slightly less speculative than the reading of tea leaves. However, one potential strategy FDA may be employing to further its policy goals is an attempt to drive a wedge between veterinarians and producers, who currently speak with more or less one voice in the U.S.¹⁰⁹ This is not the case in other countries where veterinarians are kept in high demand by stringent requirements for prescribing drugs to livestock. Thus, when FDA's Draft Guidance #209 calls for greater veterinarian involvement in all treatment decisions, one could speculate that this not only is designed as an attack on indiscriminate use of antibiotics, but also as an enticement to the veterinarian profession of a possible regulatory subsidy for their work.

Likewise, the imagination can run wild with speculation about what implicit promises, signals, or threats FDA is sending companies when urging their voluntary compliance with Draft Guidance #209, particularly the partial delisting of growth promotion. Could it be a prisoner's dilemma type of situation, where the first mover gets leniency (i.e. FDA acts only against competitors)? Could FDA be playing antibiotic manufacturers off of vaccine manufacturers? Could FDA be threatening action to totally withdraw certain drugs, but with a willingness to settle for mere withdrawal of growth-promotion purposes? Or does FDA refuse to consider any of these tactics that might call into question its integrity? Is industry duping FDA into prolonged discussions that will lead nowhere so that FDA will further delay regulatory action, as some consumer advocates fear?¹¹⁰ Perhaps only insiders know the answers to these questions; to an outsider, FDA's strategy for dealing with the threat of antibiotic resistance is far from clear, but a

¹⁰⁹ See part II.B.(2), *supra*.

¹¹⁰ See Brasher, *supra* note 107.

fascinating topic for speculation. But those of us in favor of fast action on this public health threat hope that FDA is opting for somewhat more strong-arm tactics, attempting to leverage their limited yet viable litigation resources into (somewhat) voluntary actions from a number of companies.

V. Conclusion

At bottom, the issue of antibiotic resistance in animal agriculture in modern times has come down to a battle of competing interests, which pits meat producers and drug manufacturers against practically everyone else in the general public. The economic benefits accruing to the former have, historically, been permitted to outweigh the public health risks incurred to society as a whole, and this has undoubtedly resulted in some amount of unnecessary disease and death.¹¹¹ FDA's legal policies, though once tipping strongly in favor of economic benefits, now weigh heavily in favor of public health; historical laws and regulations, however, are ossified in such a way that continues to benefit those who gain economically from the overuse of antibiotics. No easy path to changing the *status quo* exists, and it remains to be seen whether FDA's current strategy will succeed, or indeed whether FDA even has such a strategy. If not, it may take a public health crisis to coax action out of Congress, or voluntary action out of industry, to break the current regulatory stalemate.

¹¹¹ Institute of Medicine, *supra* note 83.